Ann Allergy Asthma Immunol 110 (2013) 397–401

Contents lists available at SciVerse ScienceDirect

CME review

Allergic reactions after immunization

John M. Kelso, MD

Division of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, California

ARTICLE INFO

Article history:
Received for publication December 11, 2012.
Received in revised form February 2, 2013.
Accepted for publication March 2, 2013.

INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review article in this issue and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test online at http://www.annallergy.org (click on the CME heading).
- Follow the online instructions to read the full version of the article; reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned; at this time, you will have earned up to 1.0 *AMA PRA Category 1 Credit*^{TM}. Please note that the minimum passing score on the post-test is 70%.

Release Date: June 1, 2013
Expiration Date: May 31, 2015
Estimated Time to Complete: 60 minutes
Target Audience: Physicians involved in providing patient care in the field of allergy/asthma/immunology
Learning Objectives:
At the conclusion of this activity, participants should be able to:

- Discuss the various clinical manifestations of allergic vs other immune vs nonimmune irritant reactions to vaccines
- Describe the biological properties of various vaccines that may predict those with the highest probability of causing immune-based reactions, including allergy in susceptible patients

Accreditation: The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.
Designation: The American College of Allergy, Asthma & Immunology (ACAAI) designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*^{TM}. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
Planning Committee Members:
John M. Kelso, MD (Author)
Michael S. Tankersley, MD (CME Series Editor)
Gailen D. Marshall, Jr., MD, PhD (Editor-in-Chief)
Disclosure of Relevant Financial Relationships:
J.M. Kelso, M.S. Tankersley, and G.D. Marshall, have nothing to disclose. Reviewers and Education/Editorial staff have no relevant financial relationships to disclose. No unapproved/investigative use of a product/device is discussed.
Recognition of Commercial Support: This activity has not received external commercial support.

CME Inquiries: Contact the American College of Allergy, Asthma & Immunology at education@acaai.org or 847-427-1200.

Any discussion of allergic or other adverse reactions to vaccines must begin by putting such events in context relative to the overwhelming good that vaccines do. Immunization is regarded as one of the greatest public health achievements of all time, having markedly reduced a large number of infectious diseases that previously caused widespread morbidity and mortality.[1] For most vaccine-preventable diseases, only a small number of cases occur each year because of widespread immunization.[2,3]

Reprints: John M. Kelso, MD, Division of Allergy, Asthma and Immunology, Scripps Clinic, 3811 Valley Centre Dr, San Diego, CA 92130; E-mail: kelso.john@scrippshealth.org.

1081-1206/13/$36.00 - see front matter
http://dx.doi.org/10.1016/j.anai.2013.03.001

It is possible for vaccination to lead to the complete elimination of an infectious disease. For example, the world has been declared free of smallpox as a result of vaccination.[4] Consequently, routine smallpox immunization was discontinued, although the vaccine remains available for use should smallpox be used as a weapon of war or terror.[5] However, the control of most vaccine-preventable diseases requires ongoing widespread vaccination, and when this vaccination does not occur, there are outbreaks of disease.[6] This is important relative to the evaluation of immunization allergies; although the easiest course may seem to be to simply diagnose the patient as being "allergic" to the vaccine and advise that they not receive additional doses, such an approach leaves the patient (and population) inadequately immunized and thus susceptible to these serious but vaccine-preventable infectious diseases. In most cases this disease susceptibility risk outweighs the risk of careful revaccination. Thus, it is important for patients who have had apparent allergic reactions to a vaccination or to vaccine components to undergo the thorough evaluation described herein, with the goal of becoming adequately immunized.[7] This review focuses on potentially IgE-mediated reactions to vaccines or vaccine components.

Reactions to Vaccination vs Preexisting Allergy to a Vaccine Constituent

Generally, 2 circumstances bring patients to allergists for evaluation of immunization allergy. The first is patients who have experienced what are best described as adverse events following immunization.[8] This phrase accurately captures what is being described, namely, that the patient received an immunization and subsequently experienced an adverse event. The immunization may or may not have caused the adverse event. If causal, the mechanism may or may not have been immunologic. If immunologic, the mechanism may or may not have been IgE mediated. The question being posed is whether such patients can receive additional doses of the suspect vaccine. The evaluation of such patients should include a careful history to determine whether the nature and timing of the adverse events following immunization are conceivably IgE mediated. If so, testing for IgE to the vaccine and vaccine components can help confirm the allergic mechanism and determine the culprit allergen.[7,9,10]

The other circumstance where allergists are consulted is when patients have a possible allergy to some vaccine component, such as egg, gelatin, latex, or yeast, but have never received the vaccine, perhaps because of this suspicion of a preexisting allergy. The question being posed is whether such patients can receive their first and then subsequent doses of vaccines that contain these components. The evaluation of such patients should again include a careful history to determine whether the nature and timing of their reaction to the vaccine component is conceivably IgE mediated. If so, testing again for IgE to the suspect allergen will help determine whether such an allergy is present.[7,9,10]

As with any suspected allergic event, the likelihood that it was IgE mediated is related to the nature and timing of symptoms.[11] Patients who develop cutaneous, respiratory, cardiovascular, and/or intestinal symptoms consistent with mast cell degranulation within minutes to 4 hours after an exposure may well have experienced an allergic, IgE-mediated reaction. The Brighton Collaboration case definition for anaphylaxis relative to immunization excludes timing of reaction to focus on the outcome (anaphylaxis) but acknowledges that "most cases start within 1 h of exposure."[12] This is the same type of evaluation that allergists routinely perform when patients describe adverse reactions to foods, drugs, or stinging insects. When the history suggests that the event could have been IgE mediated, it is appropriate to determine whether the patient has IgE antibodies to the vaccine and/or its components. Again, as with evaluation of other potentially allergic reactions, often skin test reagents or serum specific IgE assays are commercially available. Where such tests are not commercially available, allergists often perform skin tests with extracts made in the office.[13] Even when patients are determined to have specific IgE antibody to a vaccine and/or some vaccine component, it is still likely that they can be immunized with appropriate precautions.

History of an Apparently Allergic Reaction After Vaccination

If the patient has experienced an apparently IgE-mediated reaction to a vaccine, skin testing with the vaccine should be performed.[7,9,10] The testing should be performed with the same brand and dosage form administered before the reaction. The skin testing can be performed first by the prick method with undiluted vaccine, and if the result is negative, an intradermal skin test can be performed with the vaccine diluted 1:100 in normal saline. This 1:100 dilution has been determined to be a nonirritating concentration for most vaccines.[14] As with any form of testing, there may be false-positive or false-negative results. The sensitivity and specificity of vaccine skin testing have not been formally evaluated. Although there are reports of patients with positive vaccine skin test results who have subsequently received the vaccines uneventfully, there are no reports of patients with negative vaccine skin test results who have subsequently had reactions to the vaccines. For vaccines that contain other potential allergens, such as gelatin or egg, skin tests or serum specific IgE tests should be performed to these as well.

If the results of prick and intradermal skin tests to the vaccine are negative, the chance that the patient's prior reaction to the vaccine was IgE mediated or that the patient currently has IgE antibodies directed at a vaccine constituent are minimal. Nonetheless, in patients with histories of prior vaccine reactions, it is prudent to administer subsequent doses in the usual fashion but under observation for 30 minutes afterward, as is recommended for the administration of allergen immunotherapy.[15] At a minimum, epinephrine, intravenous fluids and needles, oxygen and mask/cannula, airway adjuncts, and stethoscope and sphygmomanometer should be available.[16]

In a patient whose prior vaccine reaction suggested an IgE-mediated mechanism, a positive vaccine skin test result supports that mechanism as the cause and increases the likelihood that subsequent administration of the same vaccine could lead to a similar reaction through the same mechanism. Even in this situation, the risk of subsequent vaccination must be weighed against its benefit, namely, reducing the risk of remaining inadequately immunized and developing the infectious disease that the vaccine might otherwise prevent.

This risk-benefit analysis may include assessment of the patient's immune status to the vaccine. Prior doses of vaccine, including the one that caused the reaction, may have generated a sufficient immune response to provide protection to the patient. Immune responses to vaccines are complex and likely involve both humeral and cellular components, but IgG antibody levels directed against the immunizing agent can be assessed as one measure of immune responsiveness to a vaccine. For many vaccines, levels of IgG antibody have been determined that correlate with protection from disease (Table 1).[7] If a patient has already developed and maintains protective levels of antibody against the immunizing agent, withholding or delaying subsequent doses may be appropriate. If the patient has not developed or maintained protective levels of antibody, this further demonstrates the need for vaccination, if possible.

In a patient whose history is consistent with an IgE-mediated reaction to a vaccine and who has a positive skin test result to that vaccine, it is appropriate to try to determine the culprit allergen (ie, the specific vaccine constituent to which the patient is allergic). This determination is important because the same

Table 1
Levels of antibody associated with protection from vaccine-preventable diseases

Vaccine	Protective level of IgG antibody
Diphtheria	≥0.1 IU/mL
Haemophilus influenzae b	≥0.15 μg/mL
Hepatitis A	≥10 mIU/mL
Hepatitis B surface antibody	≥10 mIU/mL
Measles (rubeola)	≥120 PRN titer
Polio (inactivated)	≥1:8 neutralizing antibody titer
Rabies	≥0.5 IU VNA/mL
Rubella	≥10 IU/mL
Tetanus	≥0.1 IU/mL
Yellow fever	≥0.7 IU/mL

Abbreviations: PRN, plaque reduction neutralization; VNA, virus-neutralizing antibodies.

ingredient may be found in other vaccines to which the patient may be exposed. For example, a patient who experienced an allergic reaction to the measles-mumps-rubella vaccine due to gelatin allergy might also react to varicella or influenza vaccines. The potentially allergenic substances in vaccines include gelatin, egg, yeast, and latex. Separate testing for these constituents should be performed when evaluating an allergic reaction to a vaccine that contains them.

History of an Apparently Allergic Reaction After Vaccine Constituent Exposure but no History of Vaccination Reaction

Gelatin

Gelatin is the vaccine constituent responsible for most allergic reactions to vaccines.[17–24] Although most such reports have come from Japan,[20–22] they have also come from the United States,[17,18,23] Finland,[19] and Germany.[24] Gelatin used in vaccines is of either bovine or porcine origin, which are extensively cross-reactive.[17,20,25] It is added to numerous vaccines as a stabilizer in microgram to milligram quantities (Table 2). Patients with allergic reactions to gelatin-containing vaccines should be evaluated for IgE antibody to gelatin. Serum specific IgE tests to gelatin are commercially available. Alternatively, skin prick test extract not approved by the Food and Drug Administration can be prepared locally by dissolving 1 level teaspoon of any flavor of sugared gelatin powder in 5 mL of normal saline (unsugared gelatin tends to gel at room temperature). A history of allergy to the ingestion of gelatin should be sought before giving a gelatin-containing vaccine; however, a negative history may not exclude an allergic reaction to gelatin injected with the vaccine.[20] Persons who react to gelatin on ingestion should be evaluated before administration of gelatin-containing vaccines. If the history is consistent with an immediate-type allergic reaction to gelatin and is confirmed by skin tests or serum specific IgE, skin testing should be performed with gelatin-containing vaccines before administration.[7,10] If vaccine skin test results are negative, the vaccine can be given in the usual manner, but the patient should be observed for 30 minutes afterward. If the vaccine skin test results are positive, the vaccine can be administered in graded doses under observation (Table 3).[7,10]

Table 2
Gelatin content of vaccines, 2013

Vaccine	Gelatin content
Influenza (Fluzone; Sanofi Pasteur, Swiftwater, Pennsylvania)	250 μg per 0.5-mL dose
Influenza (FluMist; MedImmune Vaccines, Gaithersburg, Maryland)	2,000 μg per 0.2-mL dose
Measles, mumps, rubella (MMRII; Merck, Whitehouse Station, New Jersey)	14,500 micrograms per 0.5 ml dose
Measles, mumps, rubella, varicella (ProQuad; Merck)	11,000 μg per 0.5-mL dose
Rabies (RabAvert; Novartis, Emeryville, California)	12,000 μg per 1.0-mL dose
Typhoid Vaccine Live Oral Ty21a (VIVOTIF; Berna, Coral Gables, Florida)	Capsule
Varicella (VARIVAX; Merck)	12,500 μg per 0.5-mL dose
Yellow fever (YF-VAX; Sanofi Pasteur)	7,500 μg per 0.5-mL dose
Zoster (ZOSTAVAX; Merck)	15,580 μg per 0.65-mL dose

Egg

Egg protein (ovalbumin) is present in measurable amounts in influenza and yellow fever vaccines. Patients with allergic reactions to egg-containing vaccines should be evaluated for IgE antibody to egg. There are commercially available skin test reagents and serum specific IgE tests to egg.

Influenza Vaccine and Egg Allergy

Influenza vaccine contains measurable quantities of egg protein (ovalbumin) and in theory could cause systemic reactions when injected into egg-allergic patients. However, 28 studies have been published involving more than 4,300 egg-allergic individuals receiving influenza vaccine without any serious reactions (no respiratory distress or hypotension) and with only a very low rate of minor reactions (hives and mild wheezing), which may not be different than the rate in non–egg-allergic controls.[7,26,27] Most of these studies have specifically included patients with histories of severe anaphylaxis (n = 656) with egg ingestion, and these patients also tolerate the vaccine. The reason that egg-allergic patients tolerate this egg-containing vaccine is likely because of its very low amount of egg protein. Three of the 4 manufacturers of injectable trivalent influenza vaccine (TIV) report the maximum amount of ovalbumin in the package insert, and the other manufacturer will provide the information on request. The claimed amounts are all less than 1 μg per 0.5-mL dose (Table 4). The measured amounts in independent laboratories are usually much lower than the claimed amounts. Although the intranasally administered live attenuated influenza vaccine (LAIV) contains a low amount of ovalbumin, all published studies to date have evaluated the injectable TIV, and thus TIV rather than LAIV should be used for egg-allergic recipients.

Both the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices and the American Academy of Pediatrics' Committee on Infectious Diseases (*Red Book*) have recently concluded that egg allergy of any severity (including anaphylaxis) is not a contraindication to the administration of influenza vaccine but rather a precaution.[28,29] The risk of not vaccinating is greater than the risk of vaccinating. Patients who report that they are egg allergic should be referred to an allergist, who can assess the current status of the patient's egg allergy (often outgrown) by history and skin or blood tests for IgE antibody to egg, but this should not delay their influenza vaccination. Skin testing egg-allergic persons with influenza vaccine before administration is not recommended because of its low sensitivity and specificity in predicting serious reactions to vaccine administration. Dividing the dose of vaccine is also not required because most even severely egg allergic patients can tolerate the full vaccine dose without reaction.

Table 3
Sample administration of a vaccine in graded doses

For a vaccine where the full dose is 0.5 mL, give the following doses at 15-minute intervals as tolerated[a]:
0.05 mL 1:10 dilution
0.05 mL full-strength
0.1 mL full-strength
0.15 mL full-strength
0.2 mL full-strength

[a]Under observation prepared to treat an anaphylactic reaction should it occur. Observe for at least 30 minutes after last dose.

Table 4
Ovalbumin content of injectable trivalent influenza vaccines approved for the 2012-2013 season

Brand name	Manufacturer	Approved ages	Ovalbumin content, μg per 0.5-mL dose[a]
Afluria	CSL Biotherapies (Merck) (King of Prussia, Pennsylvania)	≥9 years	≤1
Agriflu	Novartis (East Hanover, New Jersey)	≥18 years	≤0.4
Fluarix	GlaxoSmithKline (Philadelphia, Pennsylvania)	≥3 years	≤0.05
Flucelvax	Novartis	≥18 years	0
FluLaval	ID Biomedical Corporation of Quebec, GlaxoSmithKline (Montreal, Quebec, Canada)	≥18 years	≤1
Fluvirin	Novartis	≥4 years	≤1
Fluzone	Sanofi Pasteur	≥6 months	~0.1
Fluzone High-Dose	Sanofi Pasteur	≥65 years	~0.1

[a]Dose of 0.25 mL at 6 to 35 months and 0.5 mL at 3 years or older. Information is from package inserts except for Fluzone and Fluzone High-Dose from Sanofi Pasteur, which is available by telephone (1-800-822-2463) or e-mail (MIS.Emails@sanofipasteur.com).

All influenza vaccines available in the United States contain low amounts of ovalbumin. The only precaution is that influenza vaccine should be administered to those who are egg allergic in a setting where anaphylaxis can be recognized and immediately treated should it occur and patients should remain under observation for at least 30 minutes after vaccination. The current guidelines indicate that egg-allergic patients with a history of hives only after egg ingestion can receive influenza vaccine in a primary care physician's office provided the appropriate personnel and equipment are available, whereas those with a history of more severe reactions to egg ingestion should receive their vaccine in an allergist's office. However, given the safety profile of the vaccine even in patients with severe egg allergy, future guidelines may suggest that even these patients can receive the vaccine under observation in any medical setting prepared to recognize and treat a reaction.

Two new influenza vaccines that are not grown in eggs were recently approved for patients 18 years and older. Flucelvax[30] is prepared from virus propagated in cell culture, and Flublok[31] is recombinant hemagglutinin proteins produced in an insect cell line. These vaccines should not be used in patients younger than 18 years because some influenza vaccines have been found to be less immunogenic in certain age groups[32,33] and others have been found to have higher rates of adverse reactions in certain age groups[30] and the risk of the egg-based vaccines in egg-allergic patients is minimal.[7] If readily available, these vaccines would be preferred in egg-allergic adults. However, the opportunity to immunize an egg-allergic adult should not be missed if a non–egg-based vaccine is not readily available, in which case such patients should receive egg-based vaccine.

Yellow Fever Vaccine

Yellow fever vaccine is grown in chicken embryos and contains residual egg protein, although the amount is not stated in the package insert or available from the manufacturer.[34] Patients with allergic reactions to egg-containing vaccines should be evaluated for IgE antibody to egg. There are commercially available skin test reagents and serum specific IgE tests to egg. Persons who react to egg ingestion should be evaluated before administration of yellow fever vaccine. If the history is consistent with an immediate-type allergic reaction to egg and is confirmed by skin tests or serum specific IgE, skin testing should be performed with yellow fever vaccine before administration.[7,10,35] If vaccine skin test results are negative, the vaccine can be given in the usual manner, but the patient should be observed for 30 minutes afterward. If the vaccine skin test results are positive, the vaccine can be administered in graded doses under observation (Table 3).[7,10,35]

Yeast

Yeast protein (*Saccharomyces cerevisiae*; common baker's or brewer's yeast) is present in hepatitis B vaccines (up to 25 mg per dose) and quadrivalent human papillomavirus vaccine (less than 7 μg per dose). However, allergic reactions to these vaccines due to yeast allergy appear to be rare. A review of more than 180,000 adverse event reports to the Vaccine Adverse Event Reporting System found only 15 cases of possible anaphylactic reactions in individuals reporting yeast allergy, and these reactions may have been due to other vaccine constituents.[36] Patients with allergic reactions to yeast-containing vaccines should be evaluated for IgE antibody to yeast. There are commercially available skin test reagents and serum specific IgE tests to *S cerevisiae*. Yeast allergy itself is very rare, but if a patient has a history of clinical reactivity to baker's or brewer's yeast and a positive skin test result or serum specific IgE test result to *S cerevisiae*, it would be appropriate to test them with yeast-containing vaccines before administration.[7,10] If the vaccine skin test result is negative, the vaccine can be administered in the usual manner, but the patient should be observed for 30 minutes afterward. If the vaccine skin test is positive, consideration can be given to giving the vaccine in graded doses (Table 3).[7,10]

Latex

Natural rubber latex is present in the packaging of many vaccines, either in the vial or syringe.[37] There is a theoretical risk that administration of vaccines that have been in contact with such packaging could induce immediate-type allergic reactions in latex-allergic recipients; however, this risk appears to be minimal. A review of administering pharmaceuticals to latex-allergic patients from vials containing natural rubber latex closures stated that

Table 5
Suggested approach to patients with allergy to vaccine components

If positive skin test result or serum specific IgE antibody to allergen	Vaccine	Vaccine skin testing before administration[a]	30-Minute observation period after vaccination
Gelatin	See Table 3	Yes	Yes
Egg	Influenza	No	Yes
	Yellow fever	Yes	Yes
Yeast	Hepatitis B	Yes	Yes
	Human papillomavirus vaccine 4	Yes	Yes
Latex	http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf	No	Yes

[a]If result is positive, consider administration in graded doses.

"no published peer-reviewed reports have clearly demonstrated that a type 1 hypersensitivity reaction can be induced in a latex-allergic individual by administering a medication from a vial containing a latex closure."[38] Furthermore, a review of more than 160,000 reports to the Vaccine Adverse Event Reporting System revealed only 28 cases of possible immediate-type hypersensitivity reactions in vaccine recipients with a history of allergy to latex, and these may have been due to other vaccine constituents.[39] If a latex-allergic patient requires a vaccine where the only available preparation has a latex stopper, the stopper should be removed and the vaccine drawn up directly from the vial without passing the needle through the stopper. If the only available vaccine contains latex in the packaging that cannot be avoided, such as in a prefilled syringe, the vaccine can still be administered but the patient should be observed for at least 30 minutes afterward. Information on latex and vaccine packaging can be found at http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf.

Conclusions

Patients with suspected allergy to vaccines or vaccine components should be evaluated by an allergist. A careful history should determine the nature and timing of the reaction to the vaccine in question and other vaccines and vaccine constituents, such as gelatin, egg, yeast, and latex. If the history suggests a possible type 1, immediate-type hypersensitivity reaction, the evaluation should include evaluation for IgE antibodies to the suspect vaccine and components, either by skin testing or serum specific IgE antibody testing. If these test results are negative, subsequent doses can be given in the usual manner but with the patient observed for 30 minutes afterward. Even if these test results are positive, the risk of remaining unimmunized likely exceeds the risk of subsequent careful vaccination, with the vaccine administered in graded doses under observation. In patients whose histories and IgE antibody testing confirm allergic reactions to vaccine constituents (eg, gelatin, egg, and yeast or latex), preadministration vaccine skin testing is usually appropriate (Table 5). Again, even if such test results are positive, consideration can be given to administering the vaccine in graded doses under observation. A notable exception is the administration of influenza vaccine to egg-allergic patients in whom preadministration vaccine skin testing and dividing the dose are not necessary based on a large number of studies indicating that even severely egg-allergic patients can receive injectable influenza vaccine in the usual manner (observed for 30 minutes afterward) with a very low risk of reaction. In most cases, patients with suspected allergy to vaccines can receive subsequent vaccinations safely, allowing them to maintain protection against vaccine-preventable diseases.

References

[1] Centers for Disease Control and Prevention. Ten great public health achievements—United States, 1900-1999. *MMWR Morb Mortal Wkly Rep*. 1999;48:241–243.

[2] Centers for Disease Control and Prevention. Impact of vaccines universally recommended for children—United States, 1990-1998. *MMWR Morb Mortal Wkly Rep*. 1999;48:243–248.

[3] Centers for Disease Control and Prevention. Notifiable diseases and mortality tables. *MMWR Morb Mortal Wkly Rep*. 2012;61:621–634.

[4] Fenner F, Henderson D, Arita I. *Smallpox and Its Eradication*. Geneva, Switzerland: World Health Organization; 1988.

[5] Wharton M, Strikas RA, Harpaz R, et al. Recommendations for using smallpox vaccine in a pre-event vaccination program: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR Recommen Rep*. 2003;52:1–16.

[6] Jansen VA, Stollenwerk N, Jensen HJ, Ramsay ME, Edmunds WJ, Rhodes CJ. Measles outbreaks in a population with declining vaccine uptake. *Science*. 2003;301:804.

[7] Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130:25–43.

[8] Bonhoeffer J, Kohl K, Chen R, et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). *Vaccine*. 2002;21:298–302.

[9] Kelso JM. Adverse reactions to vaccines for infectious diseases. In: Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske RF, Simons FER, eds. *Middleton's Allergy: Principles & Practice*. 7th ed. Philadelphia, PA: Mosby; 2008:1189–1204.

[10] Wood RA, Berger M, Dreskin SC, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics*. 2008;122: e771–e777.

[11] Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.

[12] Ruggeberg JU, Gold MS, Bayas J-M, et al. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25:5675–5684.

[13] Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008;100:S1–S148.

[14] Wood RA, Setse R, Halsey N. Irritant skin test reactions to common vaccines. *J Allergy Clin Immunol*. 2007;120:478–481.

[15] Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127:S1–55.

[16] Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–480.e1–42.

[17] Kelso JM, Jones RT, Yunginger JW. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. *J Allergy Clin Immunol*. 1993;91: 867–872.

[18] Lasley MV. Anaphylaxis after booster influenza vaccine due to gelatin allergy. *Pediatr Asthma Allergy Immunol*. 2007;20:201–205.

[19] Patja A, Makinen-Kiljunen S, Davidkin I, Paunio M, Peltola H. Allergic reactions to measles-mumps-rubella vaccination. *Pediatrics*. 2001;107:E27.

[20] Sakaguchi M, Nakayama T, Inouye S. Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. *J Allergy Clin Immunol*. 1996;98:1058–1061.

[21] Sakaguchi M, Yamanaka T, Ikeda K, et al. IgE-mediated systemic reactions to gelatin included in the varicella vaccine. *J Allergy Clin Immunol*. 1997;99: 263–264.

[22] Sakaguchi M, Yoshida M, Kuroda W, Harayama O, Matsunaga Y, Inouye S. Systemic immediate-type reactions to gelatin included in Japanese encephalitis vaccines. *Vaccine*. 1997;15:121–122.

[23] Singer S, Johnson CE, Mohr R, Holowecky C. Urticaria following varicella vaccine associated with gelatin allergy. *Vaccine*. 1999;17:327–329.

[24] Zent O, Hennig R. Post-marketing surveillance of immediate allergic reactions: polygeline-based versus polygeline-free pediatric TBE vaccine. *Vaccine*. 2004;23:579–584.

[25] Bogdanovic J, Halsey NA, Wood RA, Hamilton RG. Bovine and porcine gelatin sensitivity in children sensitized to milk and meat. *J Allergy Clin Immunol*. 2009;124:1108–1110.

[26] Des Roches A, Paradis L, Gagnon R, et al. Egg-allergic patients can be safely vaccinated against influenza. *J Allergy Clin Immunol*. 2012;130:1213–1216.e1.

[27] Greenhawt MJ, Spergel JM, Rank MA, et al. Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy. *Ann Allergy Asthma Immunol*. 2012;109:426–430.

[28] Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2012-13 influenza season. *MMWR Morb Mortal Wkly Rep*. 2012;61:613–618.

[29] Committee on Infectious Diseases, American Academy of Pediatrics. Recommendations for prevention and control of influenza in children, 2012-2013. *Pediatrics*. 2012;130:780–792.

[30] FLUCELVAX [package insert]. New York, NY: Novartis; 2012.

[31] FLUBLOK [package insert]. Merdien, CT: Protein Sciences; 2013.

[32] FLUARIX (Influenza Virus Vaccine) 2010-2011 Formula [package insert]. Philadelphia, PA: GlaxoSmithKline; 2010.

[33] FLUVIRIN [package insert]. East Hanover, NJ: Novartis; 2012.

[34] Centers for Disease Control and Prevention. Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding use of CSL seasonal influenza vaccine (Afluria) in the United States during 2010-11. *MMWR Morb Mortal Wkly Rep*. 2010;59:989–992.

[35] YF-VAX [package insert]. Swiftwater, PA: Sanofi Pasteur; 2010.

[36] DiMiceli L, Pool V, Kelso JM, Shadomy SV, Iskander J, Team VAERS. Vaccination of yeast sensitive individuals: review of safety data in the US vaccine adverse event reporting system (VAERS). *Vaccine*. 2006;24:703–707.

[37] Latex in vaccine packaging. In: Atkinson W, Wolfe S, Hamborsky J, eds. Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. Washington, DC: Public Health Foundation; 2012.

[38] Hamilton RG, Brown RH, Veltri MA, et al. Administering pharmaceuticals to latex-allergic patients from vials containing natural rubber latex closures. *Am J Health Syst Pharm*. 2005;62:1822–1827.

[39] Russell M, Pool V, Kelso JM, Tomazic-Jezic VJ. Vaccination of persons allergic to latex: a review of safety data in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 2004;23:664–667.